JACC Vol. 55, No. 9, 2010
March 2, 2010:926–33

Letters to the Editor

Angiotensin-Converting Enzyme Inhibitor as a Marker, Not a Risk Factor, for Poor Prognosis

The recent paper by Miceli et al. (1) showed that, compared with those not receiving angiotensin-converting enzyme inhibitor (ACEI) therapy, patients receiving ACEI therapy had a significant short-term risk of in-hospital death, renal dysfunction, and atrial fibrillation when they underwent a coronary artery bypass grafting. Propensity score matching was applied to control confounding factors that differed between ACEI and non-ACEI patients in this observational cohort study. However, 2 epidemiological issues should be mentioned here. First, potential bias from uncontrolled confounding may arise when ACEI use itself is a marker for a condition with a poor prognosis that will trigger clinicians to use ACEI therapy. Consequently, ACEI therapy is found to be associated with an increased risk of the outcome, as this study showed. The bias cannot be easily handled by propensity score matching, which included only known clinical measures. Second, an accelerated failure time model is more suitable for analyzing the short-term outcome data than a proportional hazards model and conditional logistic regression model due to a short follow-up period. The authors should provide detailed person-time data and check the assumption of proportional hazard for ACEI use. Descriptive statistics, including survival curve plotting and tabulation, may be helpful for readers to understand the clinical scenario. A time-dependent covariate model may be incorporated for adjusting ACEI use and clinical parameters.

Clinical observational studies provide scientific knowledge that should be tested in a randomized, controlled trial setting in which confounding and bias are controlled. Therefore, before searching the biological and clinical meanings of ACEI's effect on the risk of short-term prognosis among patients undergoing a coronary bypass grafting, the authors should first address some basic epidemiological and methodological issues, including confounding by indication and event history data analysis.

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doi:10.1016/j.jacc.2009.09.059

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Reply

The aim of our study was to evaluate the effect of pre-operative angiotensin-converting enzyme inhibitor (ACEI) treatment on early outcomes after coronary artery bypass grafting (CABG) (1) by reviewing our prospectively collected institutional database. We agree that ACEI users were higher-risk patients compared with non-ACEI users; however, we identified a propensity score–matched group to perform our analysis. After matching, baseline characteristics were well balanced, without any statistical difference. Propensity scoring is simply a method for reducing the effect of selection bias and potential confounding in observational studies when randomization to treatment groups is not possible, and this was highlighted as a limitation of our study.

Survival analysis, independent of its nonparametric, semiparametric, or parametric methods, is applicable when the measure of interest is a time-related event (2). According to the current American College of Cardiology/American Heart Association guidelines for CABG, we defined as early outcomes those events occurring during the immediate hospitalization or within 30 days of surgery (3). For these reasons, our outcomes were considered as 1-time events and appropriate statistical methods were applied (4).

Observational studies can provide very valid clinical information (5) regarding "real-world" patients undergoing CABG and represent the starting point for the scientific and clinical knowledge on which randomized clinical trials are based. We do agree that the "last word" in confirming whether pre-operative ACEI treatment is a marker or a risk factor of poor early outcomes in patients undergoing CABG will come from large sample randomized studies.

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doi:10.1016/j.jacc.2009.11.043

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